Conservation of hearing by simultaneous mutation of Na,K-ATPase and NKCC1.

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Public Summary:

Scientific Abstract:
Although drug-induced and age-related hearing losses are frequent otologic problems affecting millions of people, their underlying mechanisms remain uncertain. The inner ear is exclusively endowed with a positive endocochlear potential (EP) that serves as the main driving force for the generation of receptor potential in hair cells to confer hearing. Deterioration of EP leads to hearing loss or deafness. The generation of EP relies on the activity of many ion transporters to establish active potassium (K(+)) cycling within the inner ear, including K(+) channels, the Na-K-2Cl co-transporter (NKCC1), and the alpha(1) and alpha(2) isoforms of Na,K-ATPase. We show that heterozygous deletion of either NKCC1, alpha(1)-Na,K-ATPase, or alpha(2)-Na,K-ATPase independently results in progressive, age-dependent hearing loss with minimal alteration in cochlear morphology. Double heterozygote deletion of NKCC1 with alpha(1)-Na,K-ATPase also shows a progressive, though delayed, age-dependent hearing loss. Remarkably, double heterozygote deletion of NKCC1 with alpha(2)-Na,K-ATPase demonstrates a striking preservation of hearing threshold both initially and with age. Measurements of the EP confirm the anticipated drop in potential for genotypes that demonstrate age-dependent hearing loss. The EP generated by the NKCC1 + alpha(2)-Na,K-ATPase double heterozygote, however, is maintained at a level comparable to that of the control condition, suggesting a potential advantage in this combination of ion transporter modification. These observations provide insight into the detailed mechanisms of EP generation, and results of combination-knockout experiments may have important implications in the future treatment of drug-induced and age-related hearing losses.